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Bridging studies in support of oral pediatric formulation development

Benedicte M. Ricci*

F. Hoffmann-La Roche AG, Basel, Switzerland

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ABSTRACT

Adequate pediatric formulations are a must to ensure compliance to treatment, and safe delivery of the intended dose. Adult formulations may not be suitable for children, and new pediatric formulation(s) must be developed for the pediatric studies, and for market. As the development of pediatric formulations with optimized properties for market might be challenging, preliminary "enabling" formulations might be envisaged for early pediatric studies, prior to the introduction of more elegant market formulations in the confirmatory study. Supportive clinical studies, such as relative bioavailability (RBA) studies may be necessary to establish the bridge from adult and/or enabling formulations to the final pediatric formulation. Late changes to the pediatric formulation will necessitate establishment of bioequivalence (BE) between the two drug products. As failure to demonstrate BE can delay approval, it is strongly advised that the final pediatric formulation(s) be introduced no later than in the pivotal program. RBA studies assessing performance of pediatric formulations are typically performed in adult healthy volunteers, however a possible interplay between age/disease and formulation effects must be taken into account. Formulation bridging based on in vitro approaches might be envisaged under certain circumstances, such as minor formulation changes, development of new dosage strengths, or BCS class-supported biowaivers.

1. Introduction

Appropriate pediatric drug formulations are the basis of an efficient drug therapy for children and they should allow compliance to treatment, and accurate delivery of the intended dose. They must be appropriate for each pediatric age group and disease, palatable, and convenient with minimal risk of dosing error. Dosing should be safe, in terms of both active ingredients and excipients. Depending on the pediatric age groups, adult formulations may not be suitable for use in children, and new pediatric formulation(s) must be specifically developed for the pediatric clinical studies, and for market. Development of the pediatric formulation may be technically more complex, and time and cost intensive than the adult formulation due to additional constraints with regards to choice of dosage forms, route of administration, excipients, importance of taste-masking, volume of administration, size of dosage form, and oftentimes the need for flexible dosage. In order not to delay the pediatric clinical studies and expedite the overall development of the drug product, a simple enabling formulation may play an important role in the pediatric development strategy, as it may allow rapid initiation of early, non pivotal pediatric studies (EMA, 2013a). These enabling formulations can be intermediate of the intended final pediatric formulation, or derived from existing adult market formulation. Prototypes of the market formulation may be appropriate in special cases (e.g., when the bitterness of an active drug ingredient cannot be masked in a simple formulation), however, they usually require a longer lead time. Examples of enabling formulations may be powder mixes, granulates or pellets in bottles. As enabling formulations are preliminary formulations, often requiring some degree of ad hoc preparation/manipulation, they should be optimized to more complex/elegant market-viable final formulations. A pediatric program may therefore include enabling and final pediatric formulations, differing from the adult market formulation(s), and available in suitable dosage strengths to allow dosing of children over the foreseen age/weight range. In the case of complex technical projects, development of the intended final pediatric formulation may have to be initiated in parallel to that of the enabling formulation.

To ensure a successful and efficient pediatric program, the technical development must be aligned with the clinical pediatric development. The latter is generally more streamlined than the adult drug development, as some knowledge of the drug is already available from the adult indication (Dunne et al., 2011). The FDA published a pediatric study decision tree which provides an assumption-based framework for the extrapolation of efficacy from adults to children (FDA, 2003b), and similar principles were discussed in EMA guidelines (EMA, 2001, 2006). By leveraging all available information from drug development in adults, disease,

* Correspondence address: Department of Clinical Pharmacology, F. Hoffmann-La Roche AG, Postfach, CH-4070 Basel, Switzerland. Tel.: +41 61 688 5067; fax: +41 61 688 60 07.
E-mail address: benedicte.ricci@roche.com

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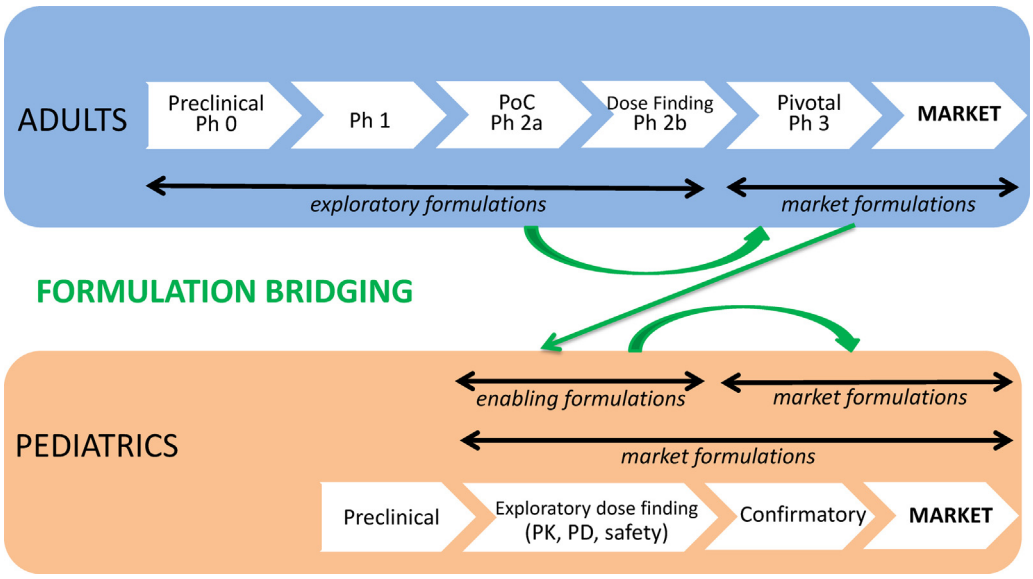

Fig. 1. Opportunities for formulation bridging in support of pediatric formulation development. Early exploratory pediatric studies (e.g., PoC or dose finding studies) may be conducted using either a simple preliminary "enabling" formulation or the already final "market" pediatric formulation. RBA studies can bridge between adult and pediatric formulations, and as appropriate, between enabling and final pediatric formulations. The use of the final pediatric formulation in the pivotal studies will avoid the need for BE studies.

response to treatment, and the physiological link between adults and children, sponsors may propose a two-step pediatric clinical program, composed of a dose finding exploratory study followed by a confirmatory pivotal study (Reigner et al., 2010). In rare cases when full extrapolation from adult data can be proposed, the pediatric indication may be granted on the basis of a sole pediatric study complementing adult patient studies (Dunne et al., 2011).

In order to support clinical extrapolation from adult to pediatric patient studies, and from exploratory pediatric study to pivotal pediatric study, several formulation bridges must be established. The first bridge will allow comparison of the pharmacokinetics of the drug in the formulation used in adult studies to that in the pediatric formulation to be used in the first pediatric study (typically an exploratory study). Additional formulation bridges may be needed if changes to the pediatric formulation are introduced, e.g., if an enabling formulation is used in early pediatric studies.

The interplay between clinical and technical development and opportunities for formulation bridging are shown in Fig. 1.

2. Pediatric formulation bridging

Formulation assessments must be performed prior to introduction of the new pediatric formulation in the clinical program. Bridging may be performed using clinical studies such as relative bioavailability (RBA) studies or bioequivalence (BE) studies, or rely solely on in vitro techniques. Guidelines on RBA and BE studies released by various Health Authorities, including those by the US FDA, Health Canada and the EMA (FDA, 2003a; Health Canada, 2012a,b; EMA, 2010), provide comprehensive details and specific requirements for design, conduct, and analysis of comparative BA studies. The aim of this document is to highlight some important features of bridging RBA or BE studies in the scope of pediatric drug development and provide some considerations on other formulation bridging options based on in vitro dissolution data or waivers.

2.1. Relative bioavailability (RBA) studies

The objective of relative BA studies is to compare the test (the new pediatric formulation) to the reference formulation, and assess how much they differ in the rate and extent to which the drug reaches the systemic circulation, without any formal statistical assessment. Their main purpose is to support and facilitate formulation development and optimization. RBA studies in pediatric drug development are proposed for comparison between adult and pediatric formulations, in order to derive the drug's pharmacokinetic (PK) parameters in the two formulations, and ultimately support dosing selection in pediatric clinical trials. RBA studies might also be proposed to compare the final pediatric formulation used in pivotal studies to simpler enabling formulation, if such formulation concept was proposed for early pediatric studies. Hence, formulation bridging in pediatric drug development might be performed with one or several RBA studies.

As in the development of medicines for adult use, RBA studies are typically designed using a randomized, two-period, two-sequence cross-over comparison of the test and reference formulations. The sample size must be calculated to provide appropriate precision in the drug's PK parameters in both formulations. However there is no requirement for rigid statistical BE criterion, as options to cope with non-bioequivalence exist (i.e., dosage adjustment or justification that the difference in exposure parameters is not expected to be clinically relevant). The washout period and PK sampling schedule must be carefully thought through, and the bioanalytical assay should be accurate and sensitive enough in order to derive informative PK parameters. Under certain circumstances, such as for drugs with very long half-life, a parallel group study can be considered. The release of the drug from the formulation is best assessed in single dose conditions, however, in special cases such as non-linear pharmacokinetics, multiple dose RBA studies may be necessary. Test and reference formulations should be compared under similar food conditions (usually fasted). Testing of the effect of food in an RBA study may be necessary, especially in the case of enabling formulation or market pediatric formulations that are intended to be sprinkled on food. Modified-release formulations should be tested both in fasted and fed conditions (FDA, 2002; EMA, 2013a) to rule out the occurrence of food effect and dose dumping. Several formulations/formulation principles may be tested in an RBA study by increasing the number of cross-over sequences. Lastly, sponsors might opt to include a preliminary assessment of the palatability of the test formulation in the RBA study as this could prove extremely valuable, notably for liquid pediatric formulations.

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